

### REMARKS

Claims 1-7, 9-11, 13, 15, 16, and 18-43 are present in the application and stand rejected. Claims 1, 28, and 30 have been amended. It is believed that Claims 1-7, 9-11, 13, 15, 16, and 18-43 are in condition for allowance in view of the foregoing amendments and the following comments. Reconsideration is requested.

#### Rejection Under 35 U.S.C. § 112.

Claim 30 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on the basis that the claim is not clear if the antibacterial composition is applied before or after the cleansing composition is rinsed from the surface. In view of the foregoing amendments to Claims 28 and 30, this rejection is believed to be moot.

#### Rejection of Claims 1-3, 5-7, 9, 13, 15, 16, 18, and 23-39 rejected under 35 U.S.C. § 103(a)

The Examiner has rejected Claims 1-3, 5-7, 9, 13, 15, 16, 18, and 23-39 under 35 U.S.C. § 103(a) as being unpatentable over Blackburn et al. (US Patent No. 5,753,614, hereafter the Blackburn '614 patent) in view of Huber et al (US Patent No. 3,758,682, hereafter the Huber '682 patent). The Examiner has cited the Blackburn '614 patent as disclosing a topical biocidal composition comprising chelating agents such as EDTA in a concentration of approximately 20 mMol (citing Column 2, lines 20-25), the inclusion of surfactants such as cocamidopropyl betaine, where the surfactants are present in an amount of about 1% (citing Column 2, lines 55-58, and example 4, TABLE 4), 50 mMol of a Tris buffer that maintains the pH of the formulation from 5-9, preferably 7.8 (citing Column 4, lines 10-25, and the examples); and nisin as an antibacterial agent in a concentration from 10-300 mg/mL (citing the examples). According to the Examiner, each of the components, the buffer, chelator, surfactant and biocide are shown to be synergistically related to one another in the reduction of bacterial populations

(citing the examples). In the Examiner's view, the Blackburn '614 patent differs from the instant claims only by disclosing a different Tris buffer compound; however, a compound is used in the same concentrations as the instant claims and for the same purpose of maintaining the pH of the formulation in a specific range. The Examiner has cited the Huber '682 patent as disclosing a formulation useful in wound healing comprising a buffer solution comprising tris(hydroxymethyl) amino methane (citing Column 13, lines 25-30) that can be administered orally contacting the oral mucosa (citing Column 24, lines 19-53). The Examiner has concluded that an artisan of ordinary skill would have been motivated to include these components in order to improve the stability of the wound treating formulation. This rejection is respectfully traversed.

The Blackburn '614 patent discloses and claims a food preservative composition comprising a lanthionine-containing bacteriocin, such as nisin, at a concentration of about 0.1 µg/ml to 300 µg/ml, and about 0.1 mM to 20 mM of a chelating agent, such as EDTA. In an optional embodiment, the food preservative composition of the Blackburn '614 patent may contain from about 0.01% to 1.0% of surfactant (see the Blackburn '614 patent, Column 2, lines 40-47). Useful surfactants are described in the Blackburn '614 patent at Column 2, lines 53-57, as follows:

[T]he nonionic surfactants Tweens, Tritons, and glycerides, ionic surfactants such as fatty acids, quaternary compounds, anionic surfactants such as sodium dodecyl sulphate and amphoteric surfactants such as cocamidopropyl betaine and emulsifiers.

Nisin is disclosed as being a preservative in dairy products, such as processed cheese, cream and milk (Column 1, lines 48-49).

In sharp contrast, the present application claims a skin cleanser comprising from 5 mM to 250 mM of a chelating agent, an amount of Tris (hydroxymethyl) aminomethane base effective to maintain the pH of the cleanser in the range of 7.0 to 9.0, and from 1 to 30% by volume of

cocamidopropyl betaine. In preferred embodiments, the applicants' skin cleanser comprises about 8 mM EDTA, about 20 mM Tris, and about 10% by volume cocamidopropyl betaine. It is important to note that in applicants' invention as claimed, the amounts of the chelating agent and the cocamidopropyl betaine relative to each other are selected to allow the chelating agent and the cocamidopropyl betaine to synergistically cooperate to enhance antimicrobial activity of the skin cleanser when in aqueous solution. There is no disclosure or remote suggestion of applicants' invention in the Blackburn '614 patent.

Blackburn further teaches that concentrations of EDTA in excess of 20 mM are inhibitory (non-potentiating) to nisin activity and suggests that the only way to reduce the EDTA inhibition is to inactivate its chelating activity with the addition of proteinaceous carriers and polyvalent polymers (containing high levels of cations), such as serum albumin, collagen, gelatin, casein, and keratin. This is confirmed in Table 7 of the Blackburn '614 patent in which nisin antibacterial activity was increased in the presence of bovine serum albumin (BSA – containing calcium ions), and in Table 14 wherein  $\text{Ca}^{2+}$  reportedly inhibited nisin activity only at a concentration above 3 mM. In contrast, the present applicants have discovered that a potentiation effect is obtained through the chelating function of buffered EDTA, and while Blackburn does not teach a mode of action, it cannot be through chelation; otherwise, the inhibition of EDTA described in the Blackburn '614 patent would not be reduced with the addition of calcium. Following the teachings in the Blackburn '614 patent, a person of ordinary skill in the art would be led to believe that wound treatment using the Blackburn composition would be ineffective in the presence of serum albumin (present in all tissues and a particularly in "seeping" wounds) – a finding that teaches directly away from applicants' invention. Thus, the enhancement of antimicrobial activity of nisin in Blackburn's composition containing EDTA and a surfactant appears to be a description of the stabilization of nisin (with some activity other than

chelation as previously described) in combination with the surfactant, which in combination with the nisin may be causing the reported result. Furthermore, the Blackburn '614 patent describes CaEDTA as a suitable replacement for EDTA in the disclosed food preservative compositions. This is in direct contrast to applicants' invention where the presence of calcium ions would act to inhibit, not enhance, the antimicrobial activity of the skin cleanser of the present claims.

For the foregoing reasons, applicants' Claims 1-3, 5-7, 9, 13, 15, 16, 18, and 23-39 would not have been obvious under 35 U.S.C. § 103(a) over the Blackburn '614 patent.

The Huber et al. '682 patent discloses pharmaceutical compositions comprising orgotein for ameliorating the adverse effects of inflammatory conditions, of stress conditions, including shock and toxemia, and of certain viral diseases. Although the Examiner has cited the Huber et al. '682 patent at Column 13, lines 25-30, as disclosing a formulation comprising tris(hydroxymethyl) amino methane as a buffer, it is respectfully submitted that the Examiner has misinterpreted this portion of the Huber et al. '682 patent. As disclosed at Column 12, line 64, through Column 13, line 34, the orgotein utilized in the composition is characterized by the isolation of orgotein from a mixture of proteins by a multiplicity of fractionation steps employing an aqueous solution at a pH of 1 to 13 in the presence of a salt of a divalent metal. The buffers disclosed are employed in the fractionation process to maintain the pH at the desired level. Accordingly, the Huber et al. '682 patent does not disclose or remotely suggest the use of tris(hydroxymethyl) amino methane in a cleanser comprising from 5 mM to 250 mM of a chelating agent, an amount of Tris (hydroxymethyl) aminomethane base effective to maintain the pH of the cleanser in the range of 7.0 to 9, and from 1 to 30% by volume of cocamidopropyl betaine, or that the concentrations of the chelating agent and the cocamidopropyl betaine are selected to allow the chelating agent and the cocamidopropyl betaine to synergistically enhance the antimicrobial activity of the skin cleanser, as required by applicants' amended claims.

Accordingly, the Huber et al. '682 patent does not overcome the deficiencies of the disclosure of the Blackburn '614 patent, as discussed in detail above.

For the foregoing reasons, Claims 1-3, 5-7, 9, 13, 15, 16, 18, and 23-39 would not have been obvious under 35 U.S.C. § 103(a) as being unpatentable over the Blackburn '614 patent in view of the Huber et al. '682 patent, and this rejection should properly be withdrawn.

Rejection of Claims 1-6, 10, 11, 13, 15, 16, 23-29, 32, and 34-37 rejected under 35 U.S.C. § 103(a).

The Examiner has rejected Claims 1-6, 10, 11, 13, 15, 16, 23-29, 32, and 34-37 under 35 U.S.C. § 103(a) as being unpatentable over the combined disclosures of the Blackburn '614 patent in view of Robertson et al (US Patent No. 4,939,135 hereafter the Robertson '135 patent). The Examiner has cited the Robertson '135 patent as disclosing a wound healing formulation and method of applying the formulation to an ocular injury (citing the abstract) wherein the formulation comprises anti-inflammatory agents such as dexamethasone and antimicrobials such as neomycin and vancomycin (citing Column 4, lines 60-65; and Column 9, lines 60-68), wherein the active agents are in a concentration from 0.5-1.0% of the total formulation (citing Column 8, lines 1-5). The formulation further comprises chelators and sorbic acid (citing Column 10, lines 60-65). According to the Examiner, the artisan of ordinary skill would be motivated to combine the components of the Blackburn '614 patent with those of the Robertson '135 patent since they both solve the same problem of wound management with cleansing compositions, and it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to form a third composition to be used for the very same purpose. It is the Examiner's position that the idea of combining them flows logically from their having been individually taught in the prior art.

The deficiencies in the disclosures of the Blackburn '614 patent are discussed in detail above, and are fully applicable to this rejection.

The Robertson et al. '135 patent is directed to compositions and methods for the treatment of corneal haze resulting from photoblation of the cornea during ophthalmic surgery. Agents used in the compositions include steroids, growth factors, basement membrane components, anti-oxidants, regulators of collagen structure, aldose reductase inhibitors, nonsteroidal antiinflammatories, immunomodulators, antiallergics, and fatty acid derivatives, which are products of the arachidonic acid cascade and antimicrobials (see Column 3, lines 16-35). The Robertson et al. '135 patent discloses at Column 10, lines 54-64, that in addition to the principal active ingredients, the disclosed wound healing modulator compositions may optionally further comprise from about 0.0001 wt. % to 1.0 wt. % of various antimicrobial preservatives, such as EDTA. It should be noted that EDTA is commonly employed in many food and drug products as an antimicrobial preservative (but not as an active, functional component as claimed in the present application). Antimicrobial preservatives are employed at low levels (substantially below 5 mM) to prevent microbial growth during product storage. Accordingly, the Robertson et al. '135 patent does not disclose or suggest a cleanser formulation comprising a chelating agent, such as EDTA, and a pH buffering agent, such as Tris, in amounts sufficient to act as active components in potentiating the antibacterial activity of the detergent, cocamidopropyl betaine, or an added antimicrobial agent, as claimed in the present application.

The Robertson et al. '135 patent does not overcome the deficiencies of the disclosure of the Blackburn '614 patent, as discussed in detail above, and Claims 1, 4, 10, and 20 would not have been obvious under 35 U.S.C. § 103(a) over the Blackburn '614 patent in view of the Robertson et al. '135 patent, and this rejection should properly be withdrawn.

Rejection of Claims 1-3, 5, 6, 9, 13, 19-22, 30-32, 34-36, 38, and 39 under 35 U.S.C. § 103(a).

The Examiner has rejected 1-3, 5, 6, 9, 13, 19-22, 30-32, 34-36, 38, and 39 under 35 U.S.C. § 103(a) as being unpatentable over the combined disclosures of the Blackburn '614 patent in view of both Mulder et al (U.S. Patent No. 5,565,189 hereafter the Mulder '189 patent) and Gehlsen (U.S. Patent No. 6,270,781 hereafter the Gehlsen '781 patent). According to the Examiner, the Mulder '189 patent teaches a method of cleaning the skin comprising the application of a cleansing composition comprising a carrier, water and aloe vera gel, a pH buffer such as sodium borate, chelators such as EDTA, vitamin E surfactants such as cocamphoacetate, and biocides such as hydroxyquinoline (citing example 1). The Examiner indicates that the method further comprises debriding the wound site, rinsing the composition after it is applied (citing Column 4, lines 45-55), the pH of the composition is between pH 6.5-6.8 (citing Column 4, lines 3-10, and the formulation includes sensitizers that relieve pain (example 1). The Examiner states that the artisan of ordinary skill in the art would have been motivated to combine the stabilizers of the Mulder '189 patent into the Blackburn '614 patent formulation since they both clean and disinfect the skin, and that the Gehlsen '781 patent discloses a topical skin composition comprising detergents, antimicrobial agents, perfumes and pigments (Column 8, lines 6-15; Column 8, lines 57-65; Column 9, lines 8-32). From this, the Examiner concludes that an artisan of ordinary skill would have been motivated to include the pigments and perfumes of the Gehlsen '781 patent with the formulation of the Blackburn '614 patent since they comprise similar components in the same field of endeavor.

The deficiencies in the disclosures of the Blackburn '614 patent are discussed in detail above and are fully applicable to this rejection.

The Mulder '189 patent discloses a non-sensitizing, over-the-counter wound cleanser composed of a carrier portion (70-90 wt% of the cleanser; Column 2, lines 28-35), an emollient portion (up to 10 wt% of the cleanser; Column 2, lines 36-46), a humectant portion (up to 10 wt% of the cleanser; Column 2, lines 47-53), a surfactant portion (up to 10 wt% of the cleanser; Column 2, lines 54-60), a preservative portion (up to 1.5 wt% of the cleanser; Column 2, lines 54-60), and a cosmetic biocide (oxyquinoline, up to 2 wt% of the cleanser; Column 3, lines 3-4).

As described in the Mulder '189 patent, the preservative portion is employed in the disclosed cleanser only to prevent microbial growth during storage. As set forth above, EDTA is commonly employed in many food and drug products as an antimicrobial preservative (but not as an active, functional component as claimed in the present application). Accordingly, the preservative portion can be 0.08-0.12 wt % sodium EDTA and 0.7-1.2 wt % alkyl paraben (Column 2, lines 61-67). In the only disclosed example, disodium EDTA is employed at a concentration of only 0.1% (Table 1, Column 4, line 38). Thus, the Mulder '189 patent discloses the use of EDTA at relatively low levels (0.08-0.12 wt. %, corresponding to about 2.1 to about 3.2 mM) as a preservative only, and does not disclose or suggest that EDTA could or should be employed at higher levels (5 mM to 250 mM) to act synergistically as an active and functional agent in a skin cleanser composition, as claimed in the present application. In addition, the pH of the cleanser of the Mulder '189 patent is maintained within the range of 6.5 to 6.8 by the addition of an alkalinizer (up to 1% (wt/wt) triethanolamine or sodium borate or an acid/conjugate base buffering system, to maintain the pH of the cleanser within the range of 6.5 to 6.8 to assist in reepithelialization of a wound site (Column 4, lines 3-16).

As described in the present application, the compositions of the present claims comprise a chelating agent, such as EDTA, and a pH buffering agent, such as Tris, in amounts sufficient to



act as active components in potentiating the antibacterial activity of the detergent, cocamidopropyl betaine, or an added antimicrobial agent. As described in the specification at page 6, lines 12-19, the detergent or antimicrobial agent(s) has increased antimicrobial activity because of the synergy with the chelating agent and maintenance of the treated area at a pH suitable for sustained antibiotic activity. The antimicrobial agent can, therefore, be used in effective doses that are less than would be required for the same level of antimicrobial activity in the absence of the chelator. The compositions of the invention are therefore useful in counteracting or preventing an infection and are effective against infections caused by drug-resistant strains of microbes. Thus, the present invention sharply contrasts with the disclosure of the Mulder '189 patent where EDTA is employed at low levels solely as a preservative to prevent microbial growth during storage and not as an active component of the composition. Presumably, EDTA as disclosed by the Mulder '189 patent could be substituted by any of a large number of non-chelating agent preservatives commonly employed in the food, beverage, and cosmetic industries to prevent contamination during storage, none of which would act synergistically to enhance antimicrobial activity of the skin cleanser as claimed in the present application.

There is no disclosure or suggestion in the Mulder '189 patent of a composition comprising 5 mM to 250 mM of a chelating agent, such as EDTA, and cocamidopropyl betaine in amounts sufficient to act as active components in potentiating the antibacterial activity of the skin cleanser at a pH in the range of 7.0 to 9.0, as in the present invention. Accordingly, the Mulder '189 patent contains no disclosure or suggestion of a skin cleanser comprising from about 5 mM to about 250 mM of a chelating agent, an amount of Tris (hydroxymethyl) aminomethane base effective to maintain the pH of the cleanser in the range of 7.0 to 9.0, and from 1 to 30% by volume of cocamidopropyl betaine, wherein the amounts of the chelating agent and the

cocamidopropyl betaine relative to each other are selected to allow the chelating agent and the cocamidopropyl betaine to synergistically cooperate to enhance antimicrobial activity of the skin cleanser when in aqueous solution, as required by the claims of the present application. The invention of applicants' claims would not have been obvious to a person of ordinary skill in the art in view of this reference.

The Gehlsen '781 patent discloses topical formulations containing compounds that reduce or inhibit the amount of reactive oxygen metabolites (ROMs) and secondary cytokines produced or released by sources within a subject to facilitate the treatment of individuals suffering from a variety of skin and mucosal conditions, such as herpes infections and photodermatitis. Although the Gehlsen '781 patent discloses that its compositions containing its ROM inhibitory compounds may contain colorants or perfumes, it does not disclose or suggest the skin cleansers of applicants' amended claims, and does nothing to overcome the deficiencies of the Blackburn '614 patent and the Mulder '189 patent, discussed in detail above. Accordingly, Claims 1-3, 5, 6, 9, 13, 19-22, 30-32, 34-36, 38, and 39 would not have been obvious under 35 U.S.C. § 103(a) over the Blackburn '614 patent in view of the Mulder '189 patent and the Gehlsen '781 patent, and this rejection should properly be withdrawn.

Rejection of Claims 40-43 under 35 U.S.C. § 103.

The Examiner has rejected Claims 40-43 under 35 U.S.C. § 103(a) as being unpatentable over the combined disclosures of the Blackburn '614 patent in view of Horn (U.S. Patent No. 5,848,700, hereafter the Horn '700 patent). Claims 40-43 relate to kits container the skin cleanser of applicants' amended claims. The Examiner has cited the Horn '700 patent as disclosing a kit comprising instructions for various applications methods including cleansing the skin of bums, cuts, wounds, and fractures (citing the claims), and concludes that it would have

been obvious to include the skin cleanser of the Blackburn '614 patent with the instructions of the Horn '700 patent since they both endeavor to treat wounds.

The deficiencies in the disclosures of the Blackburn '614 patent are discussed in detail above, and are fully applicable to this rejection.

The Horn '700 patent discloses an emergency medical care kit that comprises a carrying case approximately the size of a briefcase or small suitcase with the upper and lower sections divided into a large number of compartments by insertion of a plastic organizer with removable covers. The reverse side of each compartment cover has instructions for treating the particular emergency, while the compartment itself contains the necessary care items for that particular emergency. A hinged divider is held by snaps across the upper section of the case to help contain the contents and also provides instruction for use of the kit, some general first aid information, and a list of emergency telephone numbers.


Although the Horn '700 patent discloses a kit for medical emergencies, it does not disclose or remotely suggest the skin cleansers of applicants' claims and does not overcome the deficiencies of the Blackburn '614 patent, discussed in detail above. Accordingly, Claims 40-43 would not have been obvious under 35 U.S.C. § 103(a) over the Blackburn '614 patent in view of the Horn '700 patent.

Conclusion

In view of the foregoing amendments and comments, Claims 1-7, 9-11, 13, 15, 16, and 18-43 are believed to be in condition for allowance. Reconsideration and favorable action are requested. The Examiner is further requested to contact the applicants' representative by telephone to discuss any issues that may facilitate prosecution of the application.

Respectfully submitted,

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